Received: 31 July 2020 | Revised: 24 September 2020 | Accepted: 28 September 2020

DOI: 10.1113/EP088548

Experimental Physiology WILEY

REVIEW ARTICLE

Physiological sex differences affect the integrative response to exercise: Acute and chronic implications

Paul Ansdell[1] | Kevin Thomas[1] | Kirsty M. Hicks[1] | Sandra K. Hunter[2] | Glyn Howatson[1] | Stuart Goodall[1]

[1] Faculty of Health and Life Sciences, Northumbria University, Newcastle upon Tyne, UK

[2] Department of Physical Therapy, Marquette University, Milwaukee, WI, USA

Correspondence
Paul Ansdell, Faculty of Health and Life Sciences, Department of Sport, Exercise and Rehabilitation, Northumbria University, Newcastle upon Tyne NE1 8ST, UK.
Email: p.ansdell@northumbria.ac.uk

Edited by: Jeremy Ward

Abstract

The anatomical and physiological differences between males and females are thought to determine differences in the limits of human performance. The notion of studying sex as a biological variable has recently been emphasized in the biosciences as a vital step in enhancing human health. In this review, we contend that the effects of biological sex on acute and chronic responses must be studied and accounted for when prescribing aerobic exercise, much like any intervention targeting the optimization of physiological function. Emerging evidence suggests that the response of physiological systems to exercise differs between males and females, potentially mediating the beneficial effects in healthy and clinical populations. We highlight evidence that integrative metabolic thresholds during exercise are influenced by phenotypical sex differences throughout many physiological systems. Furthermore, we discuss evidence that female skeletal muscle is more resistant to fatigue elicited by equivalent dosages of high-intensity exercise. How the different acute responses affect the long-term trainability of males and females is considered, with discussion about tailoring exercise to the characteristics of the individual presented within the context of biological sex. Finally, we highlight the influence of endogenous and exogenous sex hormones on physiological responses to exercise in females. Sex is one of many mediating influences on the outcomes of exercise, and with careful experimental designs, physiologists can advance the collective understanding of diversity in physiology and optimize outcomes for both sexes.

KEYWORDS
exercise, fatigue, sex, training

1 | INTRODUCTION

The influence of sex has long been of interest to those concerned with human performance. In the 19th century, several prize essays were published referring to physiological functions, such as the menstrual cycle, as pathology (Hirt, 1873; Hutchins, 1875). It was also suggested that if women competed physically with men, they would experience nervous collapse and sterility (Clark, 1873). Likewise, in the 19th century, the decision of the Obstetrical Society of London to prevent women from becoming midwifery practitioners was met with praise, with women suggested to be 'unfit to bear the physical fatigues … of obstetrical practice' (Tilt, 1875). As technology has

improved, the body of empirical evidence has grown, and the previous belief that women are less resilient to physical fatigue conflicts with present-day understanding (Hunter, 2014). Despite the progress, the number of male-only studies in biological research vastly outnumbers female-only studies, particularly in physiology (~4:1); moreover, when studies have included both sexes, only one-third have factored sex into their analyses (Beery & Zucker, 2011). By highlighting evidence demonstrating that the physiological responses to exercise differ between males and females, we will outline why the inclusion of sex as a biological variable is important to consider for optimal prescription of exercise in health and disease.

When an acute bout of exercise is considered, researchers often investigate how well an individual or a population can tolerate a given intensity, in addition to the physiological systems and/or perceptions that limit performance (Enoka & Duchateau, 2016; Hunter, 2018; Hureau, Romer, & Amann, 2018; Thomas, Goodall, & Howatson, 2018). Acute exercise imposes a stress upon physiological systems that can elicit a cascade of molecular responses, which, when repeated and progressed over the course of a training programme, can lead to physiological adaptation and improved capacity for exercise (Granata, Jamnick, & Bishop, 2018). However, much like all interventions that target health improvements, the 'dosage' of exercise is important in determining training outcomes. Exercise modality, intensity, duration and frequency are all considered to mediate the adaptation elicited by a training programme (Bishop, Granata, & Eynon, 2014), in addition to the characteristics of the exercise performer(s) (Bouchard & Rankinen, 2001). The aim of this review is to highlight how biological sex influences properties of the physiological systems involved in exercise performance and how sex differences mediate the response to acute exercise. Furthermore, we detail how sex could affect adaptations to chronic exercise, with the implications for athletic performance, health and disease of males and females.

New Findings

- **What is the topic of this review?**
  We review sex differences within physiological systems implicated in exercise performance; specifically, how they integrate to determine metabolic thresholds and fatigability. Thereafter, we discuss the implications that these sex differences might have for long-term adaptation to exercise.
- **What advances does it highlight?**
  The review collates evidence from recent physiological studies that have investigated sex as a biological variable, demonstrating that the physiological response to equivalent 'dosages' of exercise is not the same in males and females; thus, highlighting the need to research diversity in physiological responses to interventions.

2 | SEX DIFFERENCES WITHIN PHYSIOLOGICAL SYSTEMS

2.1 | Skeletal muscle

The contractile apparatus of the motor pathway is ultimately responsible for force generation and human movement (Dulhunty, 2006). Reductions in the ability of skeletal muscle to produce force are frequently observed after various forms of locomotor exercise (Brownstein, Millet, & Thomas, 2020) and are considered to limit the ability of an individual to sustain a given intensity of exercise, particularly when the intensity is high (Burnley & Jones, 2018). Although the scope of the present review is not to detail all components of exercise-induced impairment to skeletal muscle contraction, we direct the reader towards previous seminal reviews of this topic (Allen, Lamb, & Westerblad, 2008; Fitts, 2008; Powers & Jackson, 2008). The characteristics of the skeletal muscle performing exercise are thought to influence energy provision, resistance to fatigue and long-term adaptability to exercise (Westerblad, Bruton, & Katz, 2010); therefore, any sex difference in these physiological qualities could influence responses to acute and chronic exercise.

One simple observation is that males possess a greater quantity of skeletal muscle than females, which contributes to greater maximal strength (Ivey et al., 2000; Lindle et al., 1997; Miller, MacDougall, Tarnopolsky, & Sale, 1993; Welle, Tawil, & Thornton, 2008). When the physiological properties of skeletal muscle are investigated, sex differences that might influence the response to exercise become apparent. Sexual dimorphisms of gene expression lead to differences in phenotypic expression, with considerable differences in the morphological composition of skeletal muscle (Welle et al., 2008). For instance, female vastus lateralis muscles are consistently shown to have a 7–23% greater proportional area of type I muscle fibres (Roepstorff et al., 2006; Simoneau & Bouchard, 1989; Staron et al., 2000). The consequences of this greater proportion of type I fibres are multifactorial; in terms of muscle metabolism during exercise, females oxidize more fat but less carbohydrate and amino acids compared with males (Tarnopolsky, 2008) and demonstrate faster oxygen uptake ($\dot{V}_{O_2}$) kinetics during moderate exercise intensities (Beltrame, Villar, & Hughson, 2017). This is probably attributable to the fact that males have greater glycolytic capacity (Esbjörnsson, Sylvén, Holm, & Jansson, 1993), whereas females have greater whole-muscle oxidative capacity (Russ, Lanza, Rothman, & Kent-Braun, 2005). Likewise, previous observations suggest that females exhibit a smaller decrease in ATP concentrations and increases in products of ATP breakdown after all-out exercise (Esbjornsson-Liljedahl, Bodin, & Jansson, 2002; Esbjörnsson-Liljedahl, Norman, Jansson, & Sundberg, 1999). Furthermore, trained males and females differ in mitochondrial oxidative function, with females demonstrating approximately one-third greater mitochondrial intrinsic respiratory rates than males

as assessed via high-resolution respirometry after muscle biopsy (Cardinale et al., 2018). Collectively, these findings imply that female skeletal muscle metabolism is more suited to resynthesizing ATP from oxidative phosphorylation during exercise, and this is explored in more detail below.

The proportional fibre-type difference between sexes also influences the contractile properties of skeletal muscle in males and females. Male skeletal muscle exhibits faster relaxation rates compared with female muscle (Hunter, Butler, Todd, Gandevia, & Taylor, 2006), consistent with a greater proportional area of type I fibres in females. Type I fibres also demonstrate slower Ca^{2+} kinetics, lower power generation and slower shortening and relaxation velocities than type II fibres (Schiaffino & Reggiani, 2011). Indeed, evidence from muscle biopsies has shown that females have a lower rate of maximal sarcoplasmic reticulum Ca^{2+}-ATPase activity than males (Harmer et al., 2014). This difference in ionic regulation of muscle contraction has been suggested to contribute to a greater fatigue resistance of female muscle during exercise (Hunter, 2014, 2016a, b) and is explored in more detail later in this review.

Lastly, haemodynamic and perfusive properties of the muscle differ between sexes, possibly affecting oxygen delivery during exercise (Beltrame et al., 2017). Vasodilatory responses of the feed arteries to exercising skeletal muscles are greater in females; for instance, the femoral artery exhibits greater vascular conductance and blood flow during incremental exercise (Parker et al., 2007). This sex difference could promote greater muscle perfusion during exercise; however, this would also depend on the capillarization of muscle. Evidence from muscle biopsies demonstrates a higher density of capillaries per unit of skeletal muscle in females compared with males in the vastus lateralis (Roepstorff et al., 2006), a key factor of aerobic exercise performance (Mitchell, Martin, Bailey, & Ferguson, 2018a; Vanhatalo et al., 2016). Collectively, evidence suggests that the metabolic, contractile and haemodynamic properties of skeletal muscle differ between males and females, which mediates the resultant response to the same 'dosage' of exercise.

2.2 | Respiratory system

In healthy males and females, the respiratory system is relatively well equipped to tolerate high intensities of exercise. Key muscles within the respiratory system, such as the diaphragm, are purportedly the most fatigue resistant of all skeletal muscles, with a high aerobic enzymatic capacity, blood supply and resistance to vasoconstriction (Dempsey, Romer, Rodman, Miller, & Smith, 2006). Furthermore, the increased recruitment of accessory inspiratory and expiratory muscles with increasing exercise intensities alleviates the workload on individual muscles, such as the diaphragm (Aliverti et al., 1997). Despite these fatigue-resistant morphologies, respiratory muscle fatigue occurs during exercise above ~80% of maximal ramp test power (Johnson, Babcock, Suman, & Dempsey, 1993), which can affect the integrative response of physiological systems implicated in exercise performance (Romer & Polkey, 2008; Sheel, Boushel, & Dempsey, 2018) and, possibly, in a different manner in males and females. Specifically, as all exercising skeletal muscles 'compete' for available cardiac output, the respiratory muscle metaboreflex initiates sympathetic vasoconstrictor outflow to exercising skeletal muscle, reducing limb blood flow (Sheel et al., 2001), ultimately exacerbating fatigue of locomotor muscles and limiting whole-body exercise performance (Harms, Wetter, Croix, Pegelow, & Dempsey, 2000; Mador & Acevedo, 1991).

Sex differences in respiratory muscle morphology and fatigue resistance are well established (Dominelli, Molgat-Seon, & Sheel, 2019; Molgat-Seon, Peters, & Sheel, 2018b; Sheel, Richards, Foster, & Guenette, 2004). Similar to skeletal muscle, females typically have smaller lungs than males (even when matched for height; Schwartz, Katz, Fegley, & Tockman, 1988), smaller airways (Dominelli et al., 2018) and different lung geometry (Torres-Tamayo et al., 2018). These morphological differences influence factors such as the work of breathing (the product of pressure and volume for each breath; W_b), respiratory efficiency and susceptibility to arterial hypoxaemia (a reduction in the oxygen concentration in arterial blood), which all amalgamate into a potentially greater central limitation to whole-body exercise performance in females. For a given minute ventilation (volume of gas expired per minute; $\dot{V}_E$), females demonstrate a greater mechanical W_b, regardless of age (Molgat-Seon et al., 2018a) or fitness level (Guenette, Witt, McKenzie, Road, & Sheel, 2007). This is considered to be a result of the smaller airway size, as the phenomenon only becomes apparent at elevated $\dot{V}_E$ (Dominelli et al., 2019). Furthermore, to support the elevated W_b in females, the absolute $\dot{V}_{O_2}$ of respiratory muscles ($\dot{V}_{O_2RM}$) is also greater at elevated $\dot{V}_E$ (Dominelli et al., 2015). Likewise, Dominelli et al. (2019) demonstrated a lower efficiency of breathing (the ratio of W_b to $\dot{V}_{O_2RM}$ at a given $\dot{V}_E$) for females compared with males. When $\dot{V}_{O_2RM}$ is expressed as a fraction of whole-body $\dot{V}_{O_2}$, females typically dedicate ~14% of whole-body $\dot{V}_{O_2}$ at maximal exercise intensities, whereas males dedicate only ~9% (Aaron, Seow, Johnson, & Dempsey, 1992; Dominelli et al., 2015). If the $\dot{V}_{O_2}$ of a muscle is directly proportional to blood flow in the Fick equation, respiratory musculature is likely to require a greater fraction of cardiac output for females (Dominelli et al. (2019). Investigation into sex differences in blood flow competition is limited, although greater demand for blood at the respiratory level is likely to have detrimental effects on locomotor muscle blood flow (Romer & Polkey, 2008; Sheel et al., 2018).

Exercise-induced arterial hypoxaemia can occur at high exercise intensities, as a result of many factors, including alveolar hypoventilation, diffusion limitation, ventilation–perfusion mismatch and cardiac and pulmonary shunt (Dempsey & Wagner, 1999). It was suggested that females might be more prone to exercise-induced arterial hypoxaemia than males owing to their smaller lung volumes, smaller airway sizes and fewer alveoli (Dominelli & Sheel, 2019; Harms et al., 1998). When matched for lung size, no sex difference was observed in pulmonary diffusive capacity (Bouwsema, Tedjasaputra, & Stickland, 2017) and ventilation–perfusion mismatch (Olfert et al., 2004). However, at a population level, the observed difference in lung size between males and females could contribute

to the greater prevalence of exercise-induced arterial hypoxaemia in females.

Despite these potentially more limiting morphologies within the female respiratory system compared with males, some functional aspects could counteract any central limitation to exercise performance. For example, the diaphragm is more fatigue resistant in females compared with males (Guenette et al., 2010; Welch, Archiza, Guenette, West, & Sheel, 2018). Furthermore, females appear to recruit extra-diaphragmatic accessory muscles at elevated $\dot{V}_E$, which could also serve to alleviate diaphragm fatigue (Mitchell, Schaeffer, Ramsook, Wilkie, & Guenette, 2018b). The greater fatigue resistance of the diaphragm appears to elicit a lower respiratory muscle metaboreflex in females compared with males, preserving lower limb blood flow and vascular resistance (Smith *et al*., 2016, 2017). The caveat exists that the findings of Smith *et al*. (2016, 2017) were after resistive breathing; therefore, whether a similar sex difference exists during whole-body exercise is currently unknown. Despite this greater fatigue resistance, the evidence regarding sex differences within the respiratory system could lead to the suggestion that central limitations to whole-body exercise performance might be greater in females. The implications of these sex differences for acute and chronic exercise prescription are discussed below in Section 4.

2.3 | Nervous system

Muscle contraction is initiated by the CNS, with muscle activation being a limiting factor to exercise performance in selected situations. Long durations of exercise are typically associated with CNS impairment (Martin et al., 2010; Thomas et al., 2014, 2016), concerning mechanisms from a variety of sites (Gandevia, 2001). Changes in neurotransmitter concentrations within the motor cortex (Meeusen & Roelands, 2018) and motoneurons (Kavanagh, McFarland, & Taylor, 2019) influence the ability to drive the muscle. Excitability of descending tracts can enhance or reduce the amount of neural drive for a given synaptic input (Sidhu et al., 2017, 2018; Weavil & Amann, 2018; Weavil, Sidhu, Mangum, Richardson, & Amann, 2016), and the firing rates of motor units can decline (Woods, Furbush, & Bigland-Ritchie, 1987). The combination of these physiological occurrences contributes to a reduction in voluntary activation (VA; Enoka, 2012), commonly measured during maximal contractions using the twitch-interpolation technique and termed central fatigue (Merton, 1954).

Voluntary activation in an unfatigued state does not differ between sexes (Ansdell et al., 2019a; Hunter et al., 2006; Keller et al., 2011; Molenaar, McNeil, Bredius, & Gandevia, 2013); however, the menstrual cycle presents a neuroendocrine interaction in females. Specifically, VA appears to be highest mid-cycle, when concentrations of neuroexcitatory oestrogen are greatest and neuroinhibitory progesterone is low, whereas in the mid-luteal phase, when progesterone concentrations are elevated, VA is lowest (Ansdell et al., 2019c). However, when exercise is performed in different phases of the menstrual cycle, the exercise-induced central fatigue does not differ (Ansdell et al., 2019c). Although this neuroendocrine interaction presents an inherent sex difference, because the cyclical changes in sex hormone concentrations do not occur within males, it appears to have minimal effects on central fatigue in response to exercise.

In terms of sex comparisons of changes in VA in response to exercise, the evidence is conflicting, which is, perhaps, a reflection of the variety of tasks used to investigate potential sex differences. After fatiguing tasks involving maximal isometric contractions, a greater reduction in VA was observed in males compared with females (Martin & Rattey, 2007; Russ & Kent-Braun, 2003; Senefeld, Pereira, Elliott, Yoon, & Hunter, 2018). Although tasks involving submaximal contractions have not demonstrated this difference in pre- *versus* postexercise values, VA showed a slower rate of decrease in females than in males during the task (Ansdell et al., 2019a). Mechanistically, this sex difference could be a combination of various neurophysiological occurrences; however, the fact that it occurs during maximal contractions could align with the hypothesis that females experience less blood flow occlusion during high-intensity contractions (Hicks, Kent-Braun, & Ditor, 2001; Hunter, Griffith, Schlachter, & Kufahl, 2009). A greater ability to maintain blood flow during maximal contractions would result in a lesser/slower accumulation of nociceptive metabolites during exercise and a subsequent reduction in activation of group III/IV afferents (Hunter, 2014). It has been suggested that activation of these neurons increases intracortical inhibition (Hilty et al., 2011; Sidhu et al., 2018) and reduces cortical and spinal excitability (Sidhu et al., 2017). These factors impair the synaptic input to the motoneuron in addition to affecting motoneuronal transmission of motor commands directly, resulting in an impaired ability to activate the muscle (Sidhu et al., 2017). Therefore, the sex difference in VA might not result from differences in intrinsic CNS properties but might instead be a reflection of slower metabolic disturbance within skeletal muscle.

Despite this, the evidence regarding the potential sex difference in CNS function during isometric contractions does little to inform our understanding of the response to whole-body exercise. As has been emphasized in the literature, in order to ascertain the neurophysiological response to an exercise task, the assessment task must be the same as the exercise task (Brownstein et al., 2018; Kalmar, 2018; Sidhu, Cresswell, & Carroll, 2013). Indeed, as discussed by Weavil and Amann (2018), corticospinal neurons are modulated by a myriad of extraneous factors, such as hydration status (Bowtell, Avenell, Hunter, & Mileva, 2013), ventilatory rate (Hopkinson et al., 2004) and arterial blood gas concentration (Hartley et al., 2016). Conceivably, any sex difference in these processes could influence the excitability and function of the CNS. Evidence has shown less of a decline in VA after cycling exercise below critical power (CP) compared with above CP, despite a lack of difference in the excitability of descending tracts between males and females (Ansdell et al., 2020). However, further investigation is required into this topic; likewise, the influence of the menstrual cycle on CNS function during exercise is currently unknown.

The motor unit is the final motor pathway of the nervous system and directly influences force production by the muscle (Del Vecchio et al., 2018, 2019). There are few studies, however, determining whether there are sex differences in motor unit behaviour. Higher

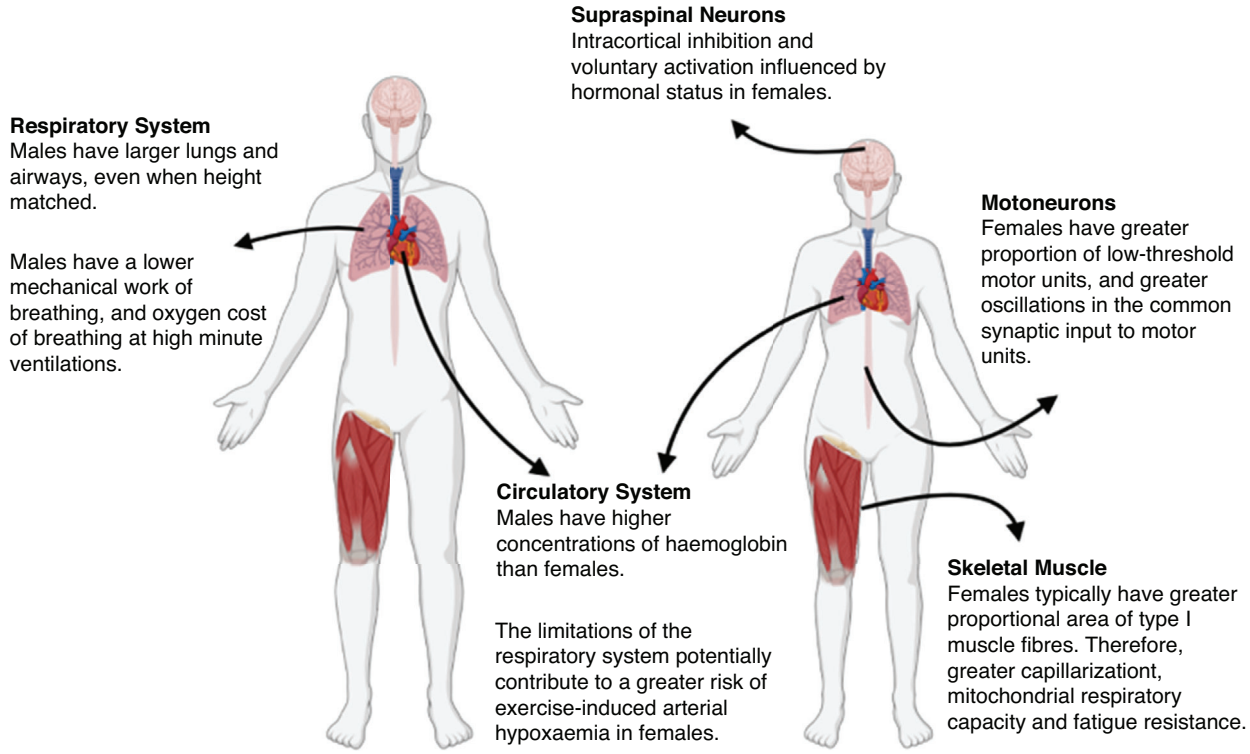

FIGURE 1 Summary of the sex differences within the key physiological systems implicated in exercise performance

discharge rates were observed in males compared with females at low (15%) contraction intensities (Harwood, Cornett, Edwards, Brown, & Jakobi, 2014), possibly owing to a lower proportion of low-threshold motor units in males compared with females (Kukulka & Clamann, 1981). These factors, amongst others, are suggested to contribute to a sex difference in force steadiness (Jakobi, Haynes, & Smart, 2018), although the authors concluded that despite a clear sex difference in steadiness, the underlying mechanisms are unclear. One recent investigation using high-density surface electromyography (Pereira et al., 2019) demonstrated no differences in discharge rate, but showed that females experienced greater oscillations in the common synaptic input to motor units. This greater coefficient of variation in the common synaptic input has been associated with the coefficient of variation of force during sustained submaximal contractions (Farina & Negro, 2015). The present challenge is to assess how the interaction between sex, motor unit firing properties and force steadiness affect functional tasks, which is challenging (Jakobi et al., 2018).

3 | SEX DIFFERENCES IN THE INTEGRATION OF PHYSIOLOGICAL SYSTEMS DURING EXERCISE

The integration of physiological systems is necessary for the regulation of homeostasis during fatiguing exercise. Performance fatigability, which is defined as a decline in an objective measure (e.g. maximal force/power production; Enoka & Duchateau, 2016; Hunter, 2018), in particular, will be determined by the cardiorespiratory and neuromuscular systems working to enhance the transport of oxygen from air to muscle for a given exercise intensity (Amann & Calbet, 2008). Although there are sex differences, from the first stages of the oxygen cascade (i.e. ventilation and gas exchange) to the final stages of oxygen usage within the muscle (see Figure 1), there is limited evidence for potential sex differences in the integrative response of physiological systems during exercise. This section will outline how sex differences in the physiological systems implicated in exercise performance integrate to determine the metabolic response to exercise, in addition to the influence that this has on commonly used tests of aerobic and anaerobic performance.

Studies investigating sex differences in performance fatigability of whole-body exercise have typically used self-paced tasks (Glace, Kremenic, & McHugh, 2013; Temesi et al., 2015). This approach, however, can hinder insight into the rate-limiting mechanisms of muscle metabolism because of differing rates of fatigue throughout a pacing strategy (de Almeida Azevedo et al., 2019). An alternative approach is constant-load exercise, with exercise intensity normalized within intensity domains, such as the power–duration relationship (see subsection 3.1), because the metabolic demands of exercise will remain consistent within and between groups. The relationship between exercise intensity and duration presents an opportunity to study the physiological mechanisms underpinning exercise performance (Jones, Vanhatalo, Burnley, Morton, & Poole, 2010) and allows mechanistic comparison between exercise tasks and even between species. For this reason, our group recently investigated the sex difference in the integrative response to exercise by using the intensity–duration relationship during single-limb isometric (Ansdell et al., 2019a) and whole-body locomotor exercise (Ansdell et al., 2020).

3.1 | The power–duration relationship

Many investigations into the power–duration relationship have been performed with male participants only, with exercise intensity typically categorized into four distinct 'domains', each of which elicits different profiles of neuromuscular fatigue (Burnley & Jones, 2018). The boundaries between domains represent transitions between mechanisms and rates of fatigability (Jones, Burnley, Black, Poole, & Vanhatalo, 2019).

Below CP (i.e. the heavy-intensity domain), metabolic responses reach a steady state, as described above, but above CP the muscle metabolic milieu increases progressively until task failure is reached (Vanhatalo, Fulford, Dimenna, & Jones, 2010). An increase in exercise intensity above CP increases the rate of muscle metabolic perturbation (Vanhatalo et al., 2010); however, the end-exercise metabolic milieu and consequent contractile dysfunction are remarkably consistent, regardless of work rate (Black et al., 2016; Jones, Wilkerson, DiMenna, Fulford, & Poole, 2008; Schäfer, Hayes, & Dekerle, 2019; Vanhatalo et al., 2010, 2016). Exercise within the severe domain terminates soon after attainment of maximal oxygen uptake ($\dot{V}_{O_2\,max}$). Exercise below CP, in the heavy-intensity domain, results in metabolic perturbation within the exercising muscle; however, this reaches a submaximal steady state and is therefore unlikely to be a limiting factor to exercise (Black et al., 2016; Jones et al., 2008; Vanhatalo et al., 2010).

This border between intensity domains is one parameter within the power–duration relationship and, together with CP, the curvature constant (*W′*) allows insight into different physiological mechanisms. The CP can be calculated from the hyperbolic relationship between exercise intensity (e.g. speed or power) and the time to task failure (Hill, 1925; Hill & Smith, 1999; Hill, Poole, & Smith, 2002; Jones et al., 2010; Monod & Scherrer, 1965); it is considered to be the greatest exercise intensity that results in 'wholly oxidative' energy provision (Poole, Burnley, Vanhatalo, Rossiter, & Jones, 2016). A crucial determinant of CP during whole-body exercise is delivery of oxygen to the skeletal muscle, and this is demonstrated by positive associations between CP and the fraction of inspired oxygen (Dekerle, Mucci, & Carter, 2012; Vanhatalo et al., 2010). Critical power is also positively correlated with the proportion of type I fibres and the muscle capillarity of knee-extensor muscles (Mitchell et al., 2018a; Vanhatalo et al., 2016). Collectively, these studies indicate that the CP is dependent on the oxygen delivery to the muscles (convective factors) and oxygen extraction and utilization within the skeletal muscle (diffusive factors).

The mechanistic link between muscle morphology and CP has implications for understanding sex differences in exercise fatigability. As previously explained, in comparison to males, females typically exhibit a greater proportional area of type I fibres and capillary density in the knee extensors (Roepstorff et al., 2006; Simoneau & Bouchard, 1989; Staron et al., 2000). During tasks where convective factors (e.g. cardiac output) are not maximized, the diffusive factors are the main determinant of CP (e.g. single-limb, isometric contractions). These characteristics of single-limb, isometric exercise provide females with an advantage over males, because a greater proportional area of type I fibres means that females possess a superior phenotype for oxidative

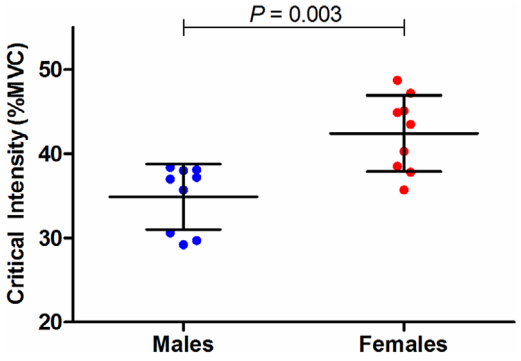

FIGURE 2 The sex difference in critical power during single-limb, intermittent, isometric exercise, from Ansdell et al. (2019a). Abbreviation: MVC, maximal voluntary contraction

metabolism and fatigue resistance (Schiaffino & Reggiani, 2011). For instance, in the internal muscle structure, type I fibres demonstrate a greater density and volume of mitochondria and a greater rate of oxidative enzyme activity (e.g. succinate dehydrogenase; Rivero, Talmadge, & Edgerton, 1998); and with regard to the extracellular surroundings, type I fibres have a greater capillary-to-fibre ratio (Andersen, 1975). These factors combine to permit metabolic differences between fibres, such as a greater ability to regenerate ATP via the tricarboxylic acid (Krebs) cycle and therefore an ability to match ATP consumption with aerobic resynthesis in type I fibres, an occurrence that is not possible in type II fibres (Schiaffino & Reggiani, 2011). This matching of consumption and aerobic resynthesis is the underlying physiological principle behind CP; thus, it is not surprising that owing to a greater proportion of type I fibres, in tasks not limited by oxygen delivery the CP is greater in females (Ansdell et al., 2019a; Figure 2).

During whole-body exercise, two elements influence the use of oxygen within working musculature: (i) convective factors, such as ventilation, cardiac output and haemoglobin concentration; and (ii) diffusive factors, such as muscle capillarity, mitochondrial density and the arteriovenous oxygen difference (Wagner, 1988, 1996). When a large muscle mass is engaged in the task (e.g. cycling or running), blood flow is distributed to different muscles and physiological systems during exercise by sympathetically mediated vasoconstriction in an attempt to maintain adequate perfusion pressures (Sheel et al., 2018), and the required skeletal muscle blood flow can exceed the pumping capacity (cardiac output) of the heart (Calbet et al., 2004). As a result, the physiological challenges during whole-body exercise are multifactorial when compared with single-limb exercise, where the quantity and magnitude of muscles recruited are far less.

The CP during whole-body exercise, however, is dependent on both oxygen delivery and utilization (Jones et al., 2010; Monod & Scherrer, 1965). This is demonstrated by experimental work showing that complete blood flow occlusion reduces abolishes CP (Broxterman et al., 2015), whereas manipulating the degree of occlusion by changing the contraction duty cycle shows a positive association between rest period duration (non-occlusion) and CP (Broxterman et al.,

2014). Additionally, individuals with impaired oxygen delivery (e.g. people with central limitations, such as chronic obstructive pulmonary disease) exhibit a severely reduced CP (Van Der Vaart et al., 2014). When this information is placed in the context of sex differences, it is important to consider the fact that females have smaller lung volumes (Schwartz et al., 1988) and lower haemoglobin concentrations (Cureton et al., 1986) compared with males. Together, these data indicate greater central limitations in females during high-intensity whole-body exercise (Harms et al., 1998), reducing oxygen delivery to the working muscle(s). Thus, the beneficial metabolic properties of female skeletal muscle (diffusive capacity) might counteract a reduced ability of females to deliver oxygen (convective capacity) relative to males during fatiguing whole-body exercise. Consequently, CP is shown to be similar between the sexes, even when expressed relative to a maximum (e.g. maximal ramp test power, P_{max}; Ansdell et al., 2020). Furthermore, recent evidence for greater mitochondrial respiration in females than in males (Cardinale et al., 2018) suggests that this is an adaptation in the oxygen cascade to compensate for a lower oxygen delivery during exercise. Accordingly, the power–duration relationship during cycling is equivalent between the sexes.

3.2 | Physiological responses to equivalent 'dosages' of exercise

Typically, when the responses of males and females are compared during constant-load exercise, the intensity is normalized to an arbitrary percentage of maximal capacity. In a single-limb model, exercise at a percentage of the maximal voluntary contraction (Ansdell, Thomas, Howatson, Hunter, & Goodall, 2018; Hunter et al., 2006, 2009) is commonly used, whereas for locomotor exercise, percentages of maximal ramp test capacity (power for cycling, P_{max}) are used (Dominelli et al., 2017; Guenette et al., 2010). Although constant-load exercise enables conclusions to be drawn about exercise work rate, normalization to arbitrary percentages of a maximum neglects the influence of metabolic thresholds. Consequently, in these studies, males and females could exercise at different work rates within an intensity domain or even in different exercise intensity domains. For example, during single-limb isometric exercise, if both sexes exercise at 50% maximal voluntary contraction (e.g. Ansdell et al., 2018), females, on average, are exercising at ~118% of critical torque and males at ~143% of critical torque (Ansdell et al., 2019a, 2019b). As is well established, exercising at increasing intensities within the severe domain leads to a faster rate of metabolic disturbance (Vanhatalo et al., 2010). Therefore, the intensity of exercise is not matched between the sexes, and task failure occurs sooner in males than in females. During cycling exercise, where CP is not different between males and females (Ansdell et al., 2020), this difference is more subtle. Within a group of well-trained participants, CP typically occurs between 70 and 80% of P_{max} (Poole, Ward, Gardner, & Whipp, 1988, 2016). If participants are subsequently studied at an intensity of 80% P_{max}, for example, this could lead to participants working at different intensities within the severe domain or within distinct intensity domains, which elicit disparate metabolic responses (Jones et al., 2008) that could impede both within- and between-group comparisons. Discussion around the pros and cons of prescribing exercise intensity relative to metabolic thresholds (Mann, Lamberts, & Lambert, 2013), and the 'optimal' metabolic threshold (Jones et al., 2019), is available elsewhere. However, to compare the performance of metabolically matched exercise intensities between the sexes, threshold normalization is probably more appropriate.

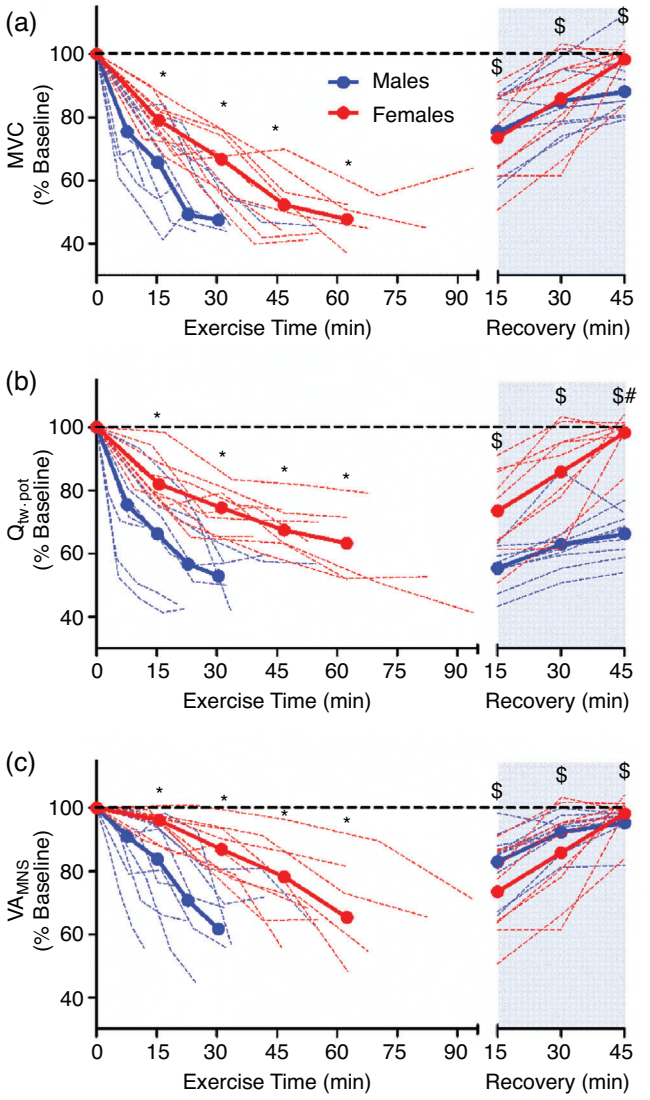

FIGURE 3 The fatigue response to exercise normalized to the critical power during single-limb, intermittent, isometric exercise. Abbreviations: MVC, maximal voluntary contraction; $Q_{tw.pot}$, potentiated quadriceps twitch force; and VA_{MNS}, voluntary activation assessed with motor nerve stimulation. Adapted from Ansdell et al. (2019a)

In two recent experiments that took the threshold normalization approach, one single-limb (Ansdell et al., 2019a) and one cycling exercise (Ansdell et al., 2020), a consistent finding was that for the same duration and intensity of exercise, females experienced approximately half the reduction in contractile function of males in the knee extensors at the end of the fatiguing exercise (e.g. Figure 3b). During single-limb exercise normalized to the critical torque, this enabled females to

exercise for approximately twice the duration before task failure (Ansdell et al., 2019a), whereas during cycling exercise, the time to task failure was similar between sexes (Ansdell et al., 2020).

The discrepancy between contractile impairment and the time to task failure in different exercise modalities is likely to be a result of different limiting factors of the two tasks. Severe-intensity exercise is thought to terminate once W' is fully utilized and a 'critical' degree of metabolic disturbance within the exercising musculature is attained (Burnley & Jones, 2018; Jones et al., 2008; Vanhatalo et al., 2010), an interpretation that explains single-limb exercise tolerance (Broxterman et al., 2015). However, for whole-body exercise, the mechanisms are less clear. In terms of the power–duration relationship, severe-intensity exercise tolerance can be explained by W'; however, as stated by Poole et al. (2016), a physiological equivalent of W' is unknown, and the nature of W' cannot be limited to a single physiological process. It is possible that the depletion of W' reflects a balance of cardiopulmonary and neuromuscular 'stress', reflecting the sensory tolerance limit of afferent information from many physiological systems (Hureau et al., 2018; Thomas et al., 2018). As suggested by Poole et al. (2016), the constituent parts of W' will differ between exercise tasks, in addition to the characteristics of the participants, which is relevant for the consideration of sex as a biological variable. Although relative W' is similar between males and females (and therefore severe-intensity time to task failure) during cycling, the reduced contractile dysfunction in females (Ansdell et al., 2020) suggests that the muscular component of W' is smaller in females than in males. Conversely, based on the elevated W_b and concurrent sensations of dyspnoea (Cory et al., 2015; Dominelli et al., 2015; Schaeffer et al., 2014), the respiratory component of W' could be greater for females. This idea is demonstrated in Figure 4. In the subsequent sections, the implications of this potential sex difference are explained for acute and chronic exercise.

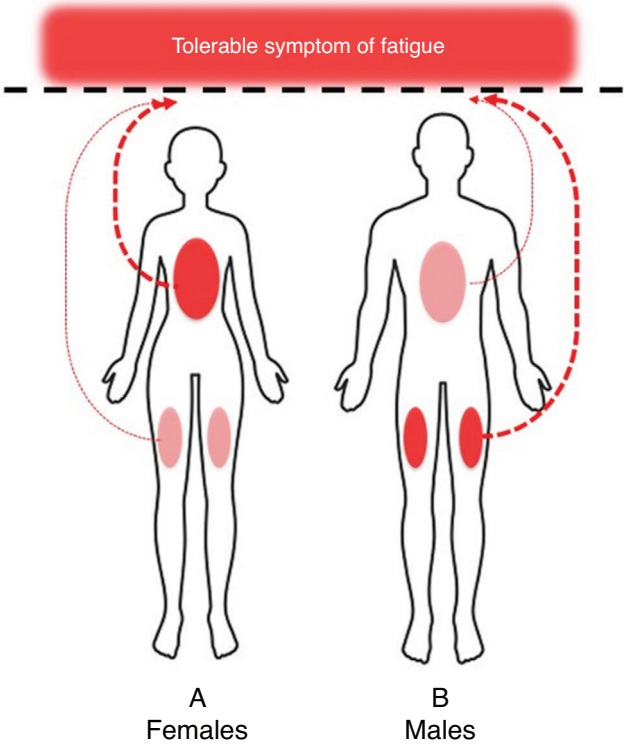

FIGURE 4 A simplified conceptual model to demonstrate that although the maximal tolerable degree of fatigue is similar between males and females, the magnitudes of its constituent parts are different. Adapted from Thomas et al. (2018)

4 | THE ACUTE AND CHRONIC IMPLICATIONS OF SEX DIFFERENCES

Optimizing the function of relevant physiological systems over the course of a training cycle is key to enhancing exercise performance, but this process relies upon the delivery of consistent, optimal, adaptive stimuli. This section will therefore discuss the mechanisms of aerobic adaptation after high-intensity exercise and how the sex differences in physiological responses during fatiguing exercise could influence this process.

High-intensity exercise induces a state of metabolic stress, the result of non-oxidative ATP resynthesis, which consists of an accumulation of metabolites and depletion of high-energy phosphate stores (Allen et al., 2008). This metabolic stress is thought to elicit long-term adaptations in the respiratory capacity of mitochondria via an increase in the electron transport system respiratory state (Jacobs et al., 2013; Lundby & Jacobs, 2016). The metabolites and the associated intracellular hypoxia provoked during high-intensity exercise are potent stimuli for activation of AMP-activated protein kinase (AMPK) and hypoxia-inducible factor α (HIF-α) pathways. Likewise, the production of reactive oxidative species is thought to stimulate peroxisome proliferator-activated receptor gamma coactivator (PGC-1α) and p38 mitogen-activated protein kinase (p38MAPK) pathways (Ji, 2007). Collectively, these signalling responses are thought to be crucial stages in mitochondrial biogenesis and angiogenesis (Marcinko & Steinberg, 2014) and to be responsible for the expression of genes involved in troponin I and myoglobin content in mice (Lin et al., 2002) and humans (Olesen, Kiilerich, & Pilegaard, 2010).

Exercise within the severe-intensity domain is associated with what is described above as metabolic stress, and disruption to the metabolic environment within the muscle could be inferred from post-exercise reductions in contractile function. Consistently in the studies by Ansdell et al. (2019a, 2020), it was demonstrated that for an equivalent duration of high-intensity exercise, females experienced less contractile dysfunction than males, potentially indicative of less disruption to the muscle metabolic environment and, perhaps, less of an adaptive stimulus for an equivalent amount of work. Evidence from proton magnetic resonance spectroscopic techniques during isometric exercise modalities would support this notion, indicating greater acidosis (Russ et al., 2005); however, equivalent data during locomotor exercise are difficult to obtain and, as yet, it is unknown whether the same phenomenon occurs.

There is a dearth of studies directly investigating the influence of sex on the adaptive signalling response after acute high-intensity exercise similar to a 'real-world' bout, such as interval training (e.g. multiple severe-intensity work periods, interspersed with moderate-intensity recovery periods or rest). However, one study comparing the acute postexercise signalling response between males and females has previously used an 'all-out' Wingate test to elicit metabolic stress, with no difference in phosphorylation of a variety of signalling molecules (Fuentes et al., 2012). It is important to note that the postexercise response to other forms of aerobic exercise in females is mediated by the hormonal status of females, with a strong oestrogenic effect (Fu, Maher, Hamadeh, Ye, & Tarnopolsky, 2009). Such an effect might have confounded the findings of Fuentes et al. (2012), because they did not control for menstrual cycle phase and they mixed eumenorrhoeic females with oral contraceptive users, two practices that have recently been deemed 'inappropriate' (Sims & Heather, 2018). When fluctuations in oestrogen were modulated, Schaumberg, Jenkins, Janse De Jonge, Emmerton, and Skinner (2017) demonstrated blunted adaptation in oral contraceptive users compared with eumenorrhoeic females after sprint interval training. Further research into the potential sex difference in postexercise signalling response is required and, as highlighted by Bishop et al. (2019), standardizing the intensity of exercise, and therefore metabolic stress, is a challenge. The use of the power–duration relationship or metabolic threshold to prescribe standardized exercise dosages can potentially help to overcome this challenge in future investigations. The aforementioned evidence also highlights the need to account for hormonal influences on the adaptive process.

Further considerations for acute exercise prescription relate to the greater rate of recovery of contractile function postexercise in females compared with males (Ansdell et al., 2019a; Senefeld et al., 2018). Forms of interval exercise relying on repeated activity close to, or exceeding, the intensity eliciting $\dot{V}_{O_2\,max}$ are based upon the notion that repeated disruption of the metabolic environment of the exercising muscle(s) will augment aerobic and anaerobic adaptation (Gibala, 2009). It is possible that females require less rest between intense interval exertions for adequate metabolic recovery; if standard training recommendations that are based predominately on male research are applied to both sexes, females might not receive an optimal stimulus for adaptation. Indeed, a recent study investigated whether manipulation of the rest period duration affects the adaptation to an interval training programme in males and females (Schmitz et al., 2020). The authors demonstrated a reduced training effect in female participants when rest periods were extended from 30 to 180 s, with no such effect in males. Therefore, manipulating the configuration of an acute bout of exercise to the characteristics of the exercise performer, whether in a clinical or an athletic setting, is necessary to elicit the maximal adaptive response. Discussion concerning whether females and males require different training stimuli to augment aerobic performance is minimal: in their recent 'Connections' article in *Experimental Physiology*, Diaz-Canestro and Montero (2020) draw an analogy between the greater oxidative capacity of females and a 'superior combustion engine', and they briefly discuss the implications of these differences within the oxygen cascade.

4.1 | Chronic exercise

Whether males and females adapt to interval training in a similar manner is not clear (Billaut & Bishop, 2009; Gibala, Gillen, & Percival, 2014). Some evidence suggests that women experience less adaptation than males in response to long-term training (Diaz-Canestro & Montero, 2019; Howden et al., 2015). When $\dot{V}_{O_2\,max}$ responses to training are compared, males demonstrate greater absolute and relative increases than females, possibly owing to differences in gene expression, lower blood volumes and blunted cardiac adaptation in females (Diaz-Canestro & Montero, 2019). Another explanatory factor might be that if females experience less metabolic stress for the same amount of high-intensity exercise, the aforementioned adaptive pathways leading to greater oxidative capacity would be activated to a lesser extent. When this is repeated throughout the course of a training programme, female $\dot{V}_{O_2\,max}$ adaptation could be lower in comparison to males as a result of less mitochondrial biogenesis and angiogenesis within the skeletal muscle.

Sex differences in genetic expression and phenotype within skeletal muscle at rest are well established (Lindholm et al., 2014; Welle et al., 2008); however, whether sex mediates the phenotypic adaptation to endurance training is not clear. One study demonstrated greater muscle protein synthesis in males 48 h after a bout of sprint interval training, and greater mitochondrial protein content in males compared with females after 3 weeks of sprint interval training (Scalzo et al., 2014), consistent with females receiving less of an adaptive stimulus from a training programme compared with males. When moderate-intensity (~60% $\dot{V}_{O_2\,max}$) continuous exercise is used as a stimulus for adaptation, studies have shown no sex difference in the long-term training response (Carter, Rennie, Hamilton, & Tarnopolsky, 2001; Hoppeler et al., 1985), perhaps implying that this phenomenon is intensity dependent.

Future research could investigate the acute responses of the molecular adaptive pathways and further interrogate the plasticity of skeletal muscle in both sexes in response to acute and chronic high-intensity exercise protocols. Tailoring the configuration of acute bouts of exercise to the characteristics of the performer is vital for achieving optimal adaptation to chronic exercise. One clinical example of where this approach has succeeded is with chronic obstructive pulmonary disease patients, who experience similar training adaptations with lesser exercise-related symptoms for interval exercise compared with continuous training (Vogiatzis, Nanas, & Roussos, 2002, 2005). Although the vast majority of evidence presented in this review is based on healthy participants, the potential for sex to mediate exercise responses in clinical populations exists; however, the interaction between disease, sex and exercise is relatively under-explored and is likely to be different between diseases. Sex differences in physiology and responses to exercise are becoming increasingly evident, and the danger is that training programmes developed and optimized

using only male data might not elicit equivalent adaptation in female populations.

5 | THE INFLUENCE OF THE MENSTRUAL CYCLE

The effects of the menstrual cycle and the hormonal fluctuations both within a cycle and throughout the female reproductive lifespan (menarche to menopause; Brown & Thomas, 2011) are not well known. Furthermore, the use of exogenous hormones to control endogenous fluctuations, such as contraceptives/therapies, has the potential to affect any physiological system containing hormone receptors, including the CNS.

Within the CNS, sex hormones can act as 'neurosteroids' and modulate neuronal function (Paul & Purdy, 1992). Where exercise is concerned, this manifests as an altered ability to activate skeletal muscle (Ansdell et al., 2019d); however, the evidence concerning maximal strength and exercise performance fatigability is equivocal (Blagrove, Bruinvels, & Pedlar, 2020; Elliott-Sale et al., 2020; McNulty et al., 2020). In terms of skeletal muscle, and independent of exercise performance, contractility (Collins et al., 2018) and fatigability (Cabelka et al., 2019) appear to be influenced by oestrogen in mouse models, although substrate metabolism during exercise is thought to be mediated by menstrual cycle phase (Oosthuyse & Bosch, 2010). Within the respiratory system, $\dot{V}_E$ and the ventilatory equivalent of carbon dioxide ($\dot{V}_E/\dot{V}_{CO_2}$) has been suggested to be increased within the luteal phase (Jurkowski, Jones, Toews, & Sutton, 1981; Schoene, Robertson, & Pierson, 1981), although this is not a consistent finding (Bemben, Salm, & Salm, 1995). Additionally, fluid regulation is altered by female sex hormone concentrations (Stachenfeld, 2008). These fluctuations within physiological systems could lead to the hypothesis that the integrative response to exercise might be altered by hormonal status, a hypothesis tested by Mattu, Iannetta, MacInnis, Doyle-Baker, and Murias (2020). The findings demonstrated no change in submaximal ($\dot{V}_{O_2}$ kinetics and the maximal lactate steady state) or maximal ($\dot{V}_{O_2\,max}$ and time to exhaustion test) responses to exercise across the menstrual cycle or between eumenorrhoeic females and combined oral contraceptive users (Mattu et al., 2020). It is important to note, however, that although metabolic thresholds and/or performance outcomes do not differ across the menstrual cycle, this does not mean that the integrative response to exercise does not change. As was demonstrated by Ansdell et al. (2020), when CP and time to exhaustion were not different between sexes, the response of physiological systems differed.

Studies investigating the menstrual cycle are becoming more abundant, particularly within the exercise sciences (Elliott-Sale et al., 2020; McNulty et al., 2020); however, as acknowledged by Elliott-Sale et al. (2020) and McNulty et al. (2020), the methodological quality of these studies is mostly poor. Recent guidelines for the study of menstrual cycle in physiology have aimed to provide researchers with a framework for ensuring that methodological considerations are observed to ensure high-quality studies (Janse de Jonge, Thompson, & Han, 2019; Sims & Heather, 2018). For now, it is important to remember that when the integrative response to exercise across the menstrual cycle is considered, absence of evidence is not evidence of absence, and careful experimental design in future will enable the effects of changing sex hormone concentrations to be discerned.

6 | CONCLUDING REMARKS

The consideration of sex in the prescription of exercise for males and females is key to optimizing adaptation in both athletic and clinical settings. Sex differences within the phenotype of physiological systems lead to differing responses to a host of interventions, and exercise is no exception. The ability to transport and utilize oxygen and differences in the fatigue resistance of contractile elements appear to contribute to the sex difference in the integrative response to an acute bout of exercise. The consequences of these sex differences in a long-term exercise programme are relatively under-researched in comparison; the possibility exists that training programmes based on data obtained from male participants leads to females receiving a potentially suboptimal exercise 'dosage'. Diversity exists across the physiological responses to a given intervention, and sex is simply one of the influencing factors in the puzzle to optimize outcomes for all. Future investigations into how the biological context of an individual influences acute and chronic physiological responses to exercise will enable optimal training patterns to be identified, promoting athletic excellence and health outcomes in all humans.

COMPETING INTERESTS

None declared.

AUTHOR CONTRIBUTIONS

All authors contributed to the intellectual content of the manuscript; P.A. drafted the manuscript; all authors revised the manuscript.

All authors read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

ORCID

Paul Ansdell https://orcid.org/0000-0001-7542-1107
Kevin Thomas https://orcid.org/0000-0003-2973-5337
Kirsty M. Hicks https://orcid.org/0000-0002-5057-9191
Sandra K. Hunter https://orcid.org/0000-0001-8013-2051
Glyn Howatson https://orcid.org/0000-0001-8494-2043
Stuart Goodall https://orcid.org/0000-0001-9029-2171

REFERENCES

Aaron, E. A., Seow, K. C., Johnson, B. D., & Dempsey, J. A. (1992). Oxygen cost of exercise hyperpnea: Implications for performance. *Journal of Applied Physiology*, *72*, 1818–1825.

Aliverti, A., Cala, S. J., Duranti, R., Ferrigno, G., Kenyon, C. M., Pedotti, A., … Yan, S. (1997). Human respiratory muscle actions and control during exercise. *Journal of Applied Physiology*, *83*, 1256–1269.

Allen, D. G., Lamb, G. D., & Westerblad, H. (2008). Skeletal muscle fatigue: Cellular mechanisms. *Physiological Reviews*, *88*, 287–332.

Amann, M., & Calbet, J. A. L. (2008). Convective oxygen transport and fatigue. *Journal of Applied Physiology*, *104*, 861–870.

Andersen, P. (1975). Capillary density in skeletal muscle of man. *Acta Physiologica Scandinavica*, *95*, 203–205.

Ansdell, P., Brownstein, C. G., Škarabot, J., Hicks, K. M., Howatson, G., Thomas, K., … Goodall, S. (2019a). Sex differences in fatigability and recovery relative to the intensity–duration relationship. *The Journal of Physiology*, *597*, 5577–5595.

Ansdell, P., Brownstein, C. G., Škarabot, J., Hicks, K. M., Howatson, G., Thomas, K., … Goodall, S. (2019b). Methodological issues influence determination of critical force during intermittent exercise: Authors' reply. *The Journal of Physiology*, *597*, 5987–5989.

Ansdell, P., Brownstein, C. G., Škarabot, J., Hicks, K. M., Simoes, D. C. M., Thomas, K., … Goodall, S. (2019c). Menstrual cycle-associated modulations in neuromuscular function and fatigability of the knee extensors in eumenorrheic women. *Journal of Applied Physiology*, *126*, 1701–1712.

Ansdell, P., Brownstein, C. G., Škarabot, J., Hicks, K. M., Simoes, D. C. M., Thomas, K., … Goodall, S. (2019d). Menstrual cycle-associated modulations in neuromuscular function and fatigability of the knee extensors in eumenorrheic females. *Journal of Applied Physiology*, *126*, 1701–1712.

Ansdell, P., Škarabot, J., Atkinson, E., Corden, S., Tygart, A., Hicks, K. M., … Goodall, S. (2020). Sex differences in fatigability following exercise normalised to the power-duration relationship. *The Journal of Physiology*, https://doi.org/10.1113/JP280031.

Ansdell, P., Thomas, K., Howatson, G., Hunter, S., & Goodall, S. (2018). Contraction intensity and sex differences in knee-extensor fatigability. *Journal of Electromyography and Kinesiology*, *37*, 68–74.

Beery, A. K., & Zucker, I. (2011). Sex bias in neuroscience and biomedical research. *Neuroscience and Biobehavioral Reviews*, *35*, 565–572.

Beltrame, T., Villar, R., & Hughson, R. L. (2017). Sex differences in the oxygen delivery, extraction, and uptake during moderate-walking exercise transition. *Applied Physiology, Nutrition and Metabolism*, *42*, 994–1000.

Bemben, D. A., Salm, P. C., & Salm, A. J. (1995). Ventilatory and blood lactate responses to maximal treadmill exercise during the menstrual cycle. *Journal of Sports Medicine and Physical Fitness*, *35*, 257–262.

Billaut, F., & Bishop, D. (2009). Muscle fatigue in males and females during multiple-sprint exercise. *Sports Medicine (Aukland, N.Z.)*, *39*, 257–278.

Bishop, D. J., Botella, J., Genders, A. J., Lee, M. J. C., Saner, N. J., Kuang, J., … Granata, C. (2019). High-intensity exercise and mitochondrial biogenesis: Current controversies and future research directions. *Physiology (Bethesda, Md.)*, *34*, 56–70.

Bishop, D. J., Granata, C., & Eynon, N. (2014). Can we optimise the exercise training prescription to maximise improvements in mitochondria function and content? *Biochimica et Biophysica Acta*, *1840*, 1266–1275.

Black, M. I., Bowtell, J. L., McDonagh, S. T. J., Blackwell, J. R., Kelly, J., Bailey, S. J., … Vanhatalo, A. (2016). Muscle metabolic and neuromuscular determinants of fatigue during cycling in different exercise intensity domains. *Journal of Applied Physiology*, *122*, 446–459.

Blagrove , R. C., Bruinvels, G., & Pedlar, C. R. (2020). Variations in strength-related measures during the menstrual cycle in eumenorrheic women: A systematic review and meta-analysis. *Journal of Science and Medicine in Sport*, https://doi.org/10.1016/j.jsams.2020.04.022.

Bouchard, C., & Rankinen, T. (2001). Individual differences in response to regular physical activity. *Medicine and Science in Sports and Exercise*, *33*, S446–S451; discussion S452–S453.

Bouwsema, M. M., Tedjasaputra, V., & Stickland, M. K. (2017). Are there sex differences in the capillary blood volume and diffusing capacity response to exercise? *Journal of Applied Physiology*, *122*, 460–469.

Bowtell, J. L., Avenell, G., Hunter, S. P., & Mileva, K. N. (2013). Effect of hypohydration on peripheral and corticospinal excitability and voluntary activation. *PLoS One*, *8*, e77004.

Brown, J. B., & Thomas, A. (2011). Types of ovarian activity in women and their significance: The continuum (a reinterpretation of early findings). *Human Reproduction Update*, *17*, 141–158.

Brownstein, C. G., Ansdell, P., Škarabot, J., Frazer, A., Kidgell, D., Howatson, G., … Thomas, K. (2018). Motor cortical and corticospinal function differ during an isometric squat compared with isometric knee extension. *Experimental Physiology*, *103*, 1251–1263.

Brownstein, C. G., Millet, G. Y., & Thomas, K. (2020). Neuromuscular responses to fatiguing locomotor exercise. *Acta Physiologica (Oxford, England)*, *n/a*, e13533.

Broxterman, R. M., Ade, C. J., Craig, J. C., Wilcox, S. L., Schlup, S. J., & Barstow, T. J. (2015). Influence of blood flow occlusion on muscle oxygenation characteristics and the parameters of the power–duration relationship. *Journal of Applied Physiology*, *118*, 880–889.

Broxterman, R. M., Ade, C. J., Wilcox, S. L., Schlup, S. J., Craig, J. C., & Barstow, T. J. (2014). Influence of duty cycle on the power–duration relationship: Observations and potential mechanisms. *Respiratory Physiology & Neurobiology*, *192*, 102–111.

Burnley, M., & Jones, A. M. (2018). Power–duration relationship: Physiology, fatigue, and the limits of human performance. *European Journal of Sport Science*, *18*, 1–12.

Cabelka, C. A., Baumann, C. W., Collins, B. C., Nash, N., Le, G., Lindsay, A., … Lowe, D. A. (2019). Effects of ovarian hormones and estrogen receptor α on physical activity and skeletal muscle fatigue in female mice. *Experimental Gerontology*, *115*, 155–164.

Calbet, J. A. L., Jensen-Urstad, M., van Hall, G., Holmberg, H.-C., Rosdahl, H., & Saltin, B. (2004). Maximal muscular vascular conductances during whole body upright exercise in humans. *The Journal of Physiology*, *558*, 319–331.

Cardinale, D. A., Larsen, F. J., Schiffer, T. A., Morales-Alamo, D., Ekblom, B., Calbet, J. A. L., … Boushel, R. (2018). Superior intrinsic mitochondrial respiration in women than in men. *Frontiers in Physiology*, *9*, 1133.

Carter, S. L., Rennie, C. D., Hamilton, S. J., & Tarnopolsky, M. A. (2001). Changes in skeletal muscle in males and females following endurance training. *Canadian Journal of Physiology and Pharmacology*, *79*, 386–392.

Clark, E. (1873). *Sex in education or, a fair chance for girls*. Boston, MA: James R. Osgood and Company.

Collins, B. C., Mader, T. L., Cabelka, C. A., Iñigo, M. R., Spangenburg, E. E., & Lowe, D. A. (2018). Deletion of estrogen receptor α in skeletal muscle results in impaired contractility in female mice. *Journal of Applied Physiology*, *124*, 980–992.

Cory, J. M., Schaeffer, M. R., Wilkie, S. S., Ramsook, A. H., Puyat, J. H., Arbour, B., … Guenette, J. A. (2015). Sex differences in the intensity and qualitative dimensions of exertional dyspnea in physically active young adults. *Journal of Applied Physiology*, *119*, 998–1006.

Cureton, K., Bishop, P., Hutchinson, P., Newland, H., Vickery, S., & Zwiren, L. (1986). Sex difference in maximal oxygen uptake. *European Journal of Applied Physiology and Occupational Physiology*, *54*, 656–660.

de Almeida Azevedo, R., Cruz, R., Couto, P., Silva-Cavalcante, M. D., Boari, D., Lima-Silva, A. E., … Bertuzzi, R. (2019). Characterization of performance fatigability during a self-paced exercise. *Journal of Applied Physiology*, *127*, 838–846.

Dekerle, J., Mucci, P., & Carter, H. (2012). Influence of moderate hypoxia on tolerance to high-intensity exercise. *European Journal of Applied Physiology*, *112*, 327–335.

Del Vecchio, A., Falla, D., Felici, F., & Farina, D. (2019). The relative strength of common synaptic input to motor neurons is not a determinant of the maximal rate of force development in humans. *Journal of Applied Physiology*, *127*, 205–214.

Del Vecchio, A., Úbeda, A., Sartori, M., Azorín, J. M., Felici, F., & Farina, D. (2018). Central nervous system modulates the neuromechanical delay in a broad range for the control of muscle force. *Journal of Applied Physiology*, *125*, 1404–1410.

Dempsey, J. A., Romer, L., Rodman, J., Miller, J., & Smith, C. (2006). Consequences of exercise-induced respiratory muscle work. *Respiratory Physiology & Neurobiology*, *151*, 242–250.

Dempsey, J. A., & Wagner, P. D. (1999). Exercise-induced arterial hypoxemia. *Journal of Applied Physiology*, *87*, 1997–2006.

Diaz-Canestro, C., & Montero, D. (2019). Sex dimorphism of VO_{2max} trainability: A systematic review and meta-analysis. *Sports Medicine (Aukland, N.Z.)*, *49*, 1949–1956.

Diaz-Canestro, C., & Montero, D. (2020). Unveiling women's powerhouse. *Experimental Physiology*, *105*, 1060–1062.

Dominelli, P. B., Molgat-Seon, Y., Griesdale, D. E. G., Peters, C. M., Blouin, J. S., Sekhon, M., … Sheel, A. W. (2017). Exercise-induced quadriceps muscle fatigue in men and women: effects of arterial oxygen content and respiratory muscle work. *The Journal of Physiology*, *595*, 5227–5244.

Dominelli, P. B., Molgat-Seon, Y., & Sheel, A. W. (2019). Sex differences in the pulmonary system influence the integrative response to exercise. *Exercise and Sport Sciences Reviews*, *47*, 142–150.

Dominelli, P. B., Render, J. N., Molgat-Seon, Y., Foster, G. E., Romer, L. M., & Sheel, A. W. (2015). Oxygen cost of exercise hyperpnoea is greater in women compared with men. *The Journal of Physiology*, *593*, 1965–1979.

Dominelli, P. B., Ripoll, J. G., Cross, T. J., Baker, S. E., Wiggins, C. C., Welch, B. T., & Joyner, M. J. (2018). Sex differences in large conducting airway anatomy. *Journal of Applied Physiology*, *125*, 960–965.

Dominelli, P. B., & Sheel, A. W. (2019). Exercise-induced arterial hypoxemia; some answers, more questions. *Applied Physiology, Nutrition and Metabolism*, *44*, 571–579.

Dulhunty, A. F. (2006). Excitation–contraction coupling from the 1950s into the new millennium. *Clinical and Experimental Pharmacology & Physiology*, *33*, 763–772.

Elliott-Sale, K. J., McNulty, K. L., Ansdell, P., Goodall, S., Hicks, K. M., Thomas, K., … Dolan, E. (2020). The effects of oral contraceptives on exercise performance in women: a systematic review and meta-analysis. *Sports Medicine (Aukland, N.Z.)*, *50*, 1785–1812.

Enoka, R. M. (2012). Muscle fatigue - from motor units to clinical symptoms. *Journal of Biomechanics*, *45*, 427–433.

Enoka, R. M., & Duchateau, J. (2016). Translating fatigue to human performance. *Medicine and Science in Sports and Exercise*, *48*, 2228–2238.

Esbjörnsson, M., Sylvén, C., Holm, I., & Jansson, E. (1993). Fast twitch fibres may predict anaerobic performance in both females and males. *International Journal of Sports Medicine*, *14*, 257–263.

Esbjornsson-Liljedahl, M., Bodin, K., & Jansson, E. (2002). Smaller muscle ATP reduction in women than in men by repeated bouts of sprint exercise. *Journal of Applied Physiology*, *93*, 1075–1083.

Esbjörnsson-Liljedahl, M., Norman, B., Jansson, E., & Sundberg, C. J. (1999). Metabolic response in type I and type II muscle fibers during a 30-s cycle sprint in men and women. *Journal of Applied Physiology*, *87*, 1326–1332.

Farina, D., & Negro, F. (2015). Common synaptic input to motor neurons, motor unit synchronization, and force control. *Exercise and Sport Sciences Reviews*, *43*, 23–33.

Fitts, R. H. (2008). The cross-bridge cycle and skeletal muscle fatigue. *Journal of Applied Physiology*, *104*, 551–558.

Fu, M.-H. H., Maher, A. C., Hamadeh, M. J., Ye, C., & Tarnopolsky, M. A. (2009). Exercise, sex, menstrual cycle phase, and 17β-estradiol influence metabolism-related genes in human skeletal muscle. *Physiological Genomics*, *40*, 34–47.

Fuentes, T., Guerra, B., Ponce-González, J. G., Morales-Alamo, D., Guadalupe-Grau, A., Olmedillas, H., … Calbet, J. A. L. (2012). Skeletal muscle signaling response to sprint exercise in men and women. *European Journal of Applied Physiology*, *112*, 1917–1927.

Gandevia, S. C. (2001). Spinal and supraspinal factors in human muscle fatigue. *Physiological Reviews*, *81*, 1725–1789.

Gibala, M. (2009). Molecular responses to high-intensity interval exercise. *Applied Physiology, Nutrition and Metabolism*, *34*, 428–432.

Gibala, M. J., Gillen, J. B., & Percival, M. E. (2014). Physiological and health-related adaptations to low-volume interval training: influences of nutrition and sex. *Sports Medicine (Aukland, N.Z.)*, *44*(Suppl 2), 127–137.

Glace, B. W., Kremenic, I. J., & McHugh, M. P. (2013). Sex differences in central and peripheral mechanisms of fatigue in cyclists. *European Journal of Applied Physiology*, *113*, 1091–1098.

Granata, C., Jamnick, N. A., & Bishop, D. J. (2018). Principles of exercise prescription, and how they influence exercise-induced changes of transcription factors and other regulators of mitochondrial biogenesis. *Sports Medicine (Aukland, N.Z.)*, *48*, 1541–1559.

Guenette, J. A., Romer, L. M., Querido, J. S., Chua, R., Eves, N. D., Road, J. D., … Sheel, A. W. (2010). Sex differences in exercise-induced diaphragmatic fatigue in endurance-trained athletes. *Journal of Applied Physiology*, *109*, 35–46.

Guenette, J. A., Witt, J. D., McKenzie, D. C., Road, J. D., & Sheel, A. W. (2007). Respiratory mechanics during exercise in endurance-trained men and women. *The Journal of Physiology*, *581*, 1309–1322.

Harmer, A. R., Ruell, P. A., Hunter, S. K., McKenna, M. J., Thom, J. M., Chisholm, D. J., & Flack, J. R. (2014). Effects of type 1 diabetes, sprint training and sex on skeletal muscle sarcoplasmic reticulum Ca^{2+} uptake and Ca^{2+}-ATPase activity. *The Journal of Physiology*, *592*, 523–535.

Harms, C. A., McClaran, S. R., Nickele, G. A., Pegelow, D. F., Nelson, W. B., & Dempsey, J. A. (1998). Exercise-induced arterial hypoxaemia in healthy young women. *The Journal of Physiology*, *507*, 619–628.

Harms, C. A., Wetter, T. J., St. Croix CM, Pegelow, D. F., & Dempsey, J. A. (2000). Effects of respiratory muscle work on exercise performance. *Journal of Applied Physiology*, *89*, 131–138.

Hartley, G. L., Watson, C. L., Ainslie, P. N., Tokuno, C. D., Greenway, M. J., Gabriel, D. A., … Cheung, S. S. (2016). Corticospinal excitability is associated with hypocapnia but not changes in cerebral blood flow. *The Journal of Physiology*, *594*, 3423–3437.

Harwood, B., Cornett, K. M. D., Edwards, D. L., Brown, R. E., & Jakobi, J. M. (2014). The effect of tendon vibration on motor unit activity, intermuscular coherence and force steadiness in the elbow flexors of males and females. *Acta Physiologica (Oxford, England)*, *211*, 597–608.

Hicks, A. L., Kent-Braun, J., & Ditor, D. S. (2001). Sex differences in human skeletal muscle fatigue. *Exercise and Sport Sciences Reviews*, *29*, 109–112.

Hill, A. V. (1925). The physiological basis of athletic records. *Lancet*, *206*, 481–486.

Hill, D. W., Poole, D. C., & Smith, J. C. (2002). The relationship between power and the time to achieve $\dot{V}O_{2max}$. *Medicine & Science in Sports & Exercise*, *34*, 709–714.

Hill, D. W., & Smith, J. C. (1999). Determination of critical power by pulmonary gas exchange. *Canadian Journal of Applied Physiology*, *24*, 74–86.

Hilty, L., Lutz, K., Maurer, K., Rodenkirch, T., Spengler, C. M., Boutellier, U., … Amann, M. (2011). Spinal opioid receptor-sensitive muscle afferents contribute to the fatigue-induced increase in intracortical inhibition in healthy humans. *Experimental Physiology*, *96*, 505–517.

Hirt (1873). *Die Gewerbeliche Thatigkeit der Frauen.* https://www.digitales-deutsches-frauenarchiv.de/meta-objekt/die-gewerblichethaetigkeit-der-frauen-vom-hygienischen-standpunkte-aus--mit-speciellen-hinweisen-auf-die-an-eine-fabrikgesetzgebung-zustellenden-anforderungen/15357addf.

Hopkinson, N. S., Sharshar, T., Ross, E. T., Nickol, A. H., Dayer, M. J., Porcher, R., … Polkey, M. I. (2004). Corticospinal control of respiratory muscles in chronic obstructive pulmonary disease. *Respiratory Physiology & Neurobiology*, *141*, 1–12.

Hoppeler, H., Howald, H., Conley, K., Lindstedt, S. L., Claassen, H., Vock, P., & Weibel, E. R. (1985). Endurance training in humans: aerobic capacity and structure of skeletal muscle. *Journal of Applied Physiology*, *59*, 320–327.

Howden, E. J., Perhonen, M., Peshock, R. M., Zhang, R., Arbab-Zadeh, A., Adams-Huet, B., & Levine, B. D. (2015). Females have a blunted cardiovascular response to one year of intensive supervised endurance training. *Journal of Applied Physiology*, *119*, 37–46.

Hunter, S. K. (2009). Sex differences and mechanisms of task-specific muscle fatigue. *Exercise and Sport Sciences Reviews*, *37*, 113–122.

Hunter, S. K. (2014). Sex differences in human fatigability: Mechanisms and insight to physiological responses. *Acta Physiologica (Oxford, England)*, *210*, 768–789.

Hunter, S. K. (2016a). Sex differences in fatigability of dynamic contractions. *Experimental Physiology*, *101*, 250–255.

Hunter, S. K. (2016b). The relevance of sex differences in performance fatigability. *Medicine and Science in Sports and Exercise*, *48*, 2247–2256.

Hunter, S. K. (2018). Performance fatigability: mechanisms and task specificity. *Cold Spring Harbor Perspectives in Medicine*, *8*, a029728.

Hunter, S. K., Butler, J. E., Todd, G., Gandevia, S. C., & Taylor, J. L. (2006). Supraspinal fatigue does not explain the sex difference in muscle fatigue of maximal contractions. *Journal of Applied Physiology*, *101*, 1036–1044.

Hunter, S. K., Griffith, E. E., Schlachter, K. M., & Kufahl, T. D. (2009). Sex differences in time to task failure and blood flow for an intermittent isometric fatiguing contraction. *Muscle & Nerve*, *39*, 42–53.

Hureau, T. J., Romer, L. M., & Amann, M. (2018). The 'sensory tolerance limit': A hypothetical construct determining exercise performance? *European Journal of Sport Science*, *18*, 13–24.

Hutchins (1875). Merrit H Cash Prize Essay, 112–168. https://babel.hathitrust.org/cgi/pt?id=mdp.39015054506475&view=1up&seq=183&q1=hutchins.

Ivey, F. M., Tracy, B. L., Lemmer, J. T., NessAiver, M., Metter, E. J., Fozard, J. L., & Hurley, B. F. (2000). Effects of strength training and detraining on muscle quality: age and gender comparisons. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *55*, B152–B157; discussion B158–B159.

Jacobs, R. A., Flück, D., Bonne, T. C., Bürgi, S., Christensen, P. M., Toigo, M., & Lundby, C. (2013). Improvements in exercise performance with high-intensity interval training coincide with an increase in skeletal muscle mitochondrial content and function. *Journal of Applied Physiology*, *115*, 785–793.

Jakobi, J. M., Haynes, E. M. K., & Smart, R. R. (2018). Is there sufficient evidence to explain the cause of sexually dimorphic behaviour in force steadiness? *Applied Physiology, Nutrition and Metabolism*, *43*, 1207–1214.

Janse de Jonge, X., Thompson, B., & Han, A. (2019). Methodological recommendations for menstrual cycle research in sports and exercise. *Medicine and Science in Sports and Exercise*, *51*, 2610–2617.

Ji, L. L. (2007). Antioxidant signaling in skeletal muscle: A brief review. *Experimental Gerontology*, *42*, 582–593.

Johnson, B. D., Babcock, M. A., Suman, O. E., & Dempsey, J. A. (1993). Exercise-induced diaphragmatic fatigue in healthy humans. *The Journal of Physiology*, *460*, 385–405.

Jones, A. M., Burnley, M., Black, M. I., Poole, D. C., & Vanhatalo, A. (2019). The maximal metabolic steady state: Redefining the 'gold standard.' *Physiological Reports*, *7*, e14098.

Jones, A. M., Vanhatalo, A., Burnley, M., Morton, R. H., & Poole, D. C. (2010). Critical power: implications for determination of $\dot{V}_{O_2\,max}$ and exercise tolerance. *Medicine and Science in Sports and Exercise*, *42*, 1876–1890.

Jones, A. M., Wilkerson, D. P., DiMenna, F., Fulford, J., & Poole, D. C. (2008). Muscle metabolic responses to exercise above and below the "critical power" assessed using ^{31}P-MRS. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *294*, R585–R593.

Jurkowski, J. E. H., Jones, N. L., Toews, C. J., & Sutton, J. R. (1981). Effects of menstrual cycle on blood lactate, O_2 delivery, and performance during exercise. *Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology*, *51*, 1493–1499.

Kalmar, J. M. (2018). On task: Considerations and future directions for studies of corticospinal excitability in exercise neuroscience and related disciplines. *Applied Physiology, Nutrition and Metabolism*, *43*, 1113–1121.

Kavanagh, J. J., McFarland, A. J., & Taylor, J. L. (2019). Enhanced availability of serotonin increases activation of unfatigued muscle but exacerbates central fatigue during prolonged sustained contractions. *The Journal of Physiology*, *597*, 319–332.

Keller, M. L., Pruse, J., Yoon, T., Schlinder-Delap, B., Harkins, A., & Hunter, S. K. (2011). Supraspinal fatigue is similar in men and women for a low-force fatiguing contraction. *Medicine and Science in Sports and Exercise*, *43*, 1873–1883.

Kukulka, C. G., & Clamann, H. P. (1981). Comparison of the recruitment and discharge properties of motor units in human brachial biceps and adductor pollicis during isometric contractions. *Brain Research*, *219*, 45–55.

Lin, J., Wu, H., Tarr, P. T., Zhang, C. Y., Wu, Z., Boss, O., … Spiegelman, B. M. (2002). Transcriptional co-activator PGC-1α drives the formation of slow-twitch muscle fibres. *Nature*, *418*, 797–801.

Lindholm, M. E., Huss, M., Solnestam, B. W., Kjellqvist, S., Lundeberg, J., & Sundberg, C. J. (2014). The human skeletal muscle transcriptome: Sex differences, alternative splicing, and tissue homogeneity assessed with RNA sequencing. *FASEB Journal*, *28*, 4571–4581.

Lindle, R. S., Metter, E. J., Lynch, N. A., Fleg, J. L., Fozard, J. L., Tobin, J., … Hurley, B. F. (1997). Age and gender comparisons of muscle strength in 654 women and men aged 20–93 yr. *Journal of Applied Physiology*, *83*, 1581–1587.

Lundby, C., & Jacobs, R. A. (2016). Adaptations of skeletal muscle mitochondria to exercise training. *Experimental Physiology*, *101*, 17–22.

Mador, M. J., & Acevedo, F. A. (1991). Effect of respiratory muscle fatigue on subsequent exercise performance. *Journal of Applied Physiology*, *70*, 2059–2065.

Mann, T., Lamberts, R. P., & Lambert, M. I. (2013). Methods of prescribing relative exercise intensity: Physiological and practical considerations. *Sports Medicine (Aukland, N.Z.)*, *43*, 613–625.

Marcinko, K., & Steinberg, G. R. (2014). The role of AMPK in controlling metabolism and mitochondrial biogenesis during exercise. *Experimental Physiology*, *99*, 1581–1585.

Martin, P. G., & Rattey, J. (2007). Central fatigue explains sex differences in muscle fatigue and contralateral cross-over effects of maximal contractions. *Pflügers Archiv: European Journal of Physiology*, *454*, 957–969.

Martin, V., Kerhervé, H., Messonnier, L. A., Banfi, J.-C., Geyssant, A., Bonnefoy, R., … Millet, G. Y. (2010). Central and peripheral contributions to neuromuscular fatigue induced by a 24-h treadmill run. *Journal of Applied Physiology*, *108*, 1224–1233.

Mattu, A. T., Iannetta, D., MacInnis, M. J., Doyle-Baker, P. K., & Murias, J. M. (2020). Menstrual and oral contraceptive cycle phases do not affect submaximal and maximal exercise responses. *Scandinavian Journal of Medicine & Science in Sports*, *30*, 472–484.

McNulty, K. L., Elliott-Sale, K. J., Dolan, E., Swinton, P. A., Ansdell, P., Goodall, S., … Hicks, K. M. (2020). The effects of menstrual cycle phase on exercise performance in eumenorrheic women: A systematic review and meta-analysis. *Sports Medicine (Aukland, N.Z.)*, *50*, 1813–1827.

Meeusen, R., & Roelands, B. (2018). Fatigue: Is it all neurochemistry? *European Journal of Sport Science*, *18*, 37–46.

Merton, P. A. (1954). Voluntary strength and fatigue. *The Journal of Physiology*, *123*, 553–564.

Miller, A. E. J., MacDougall, J. D., Tarnopolsky, M. A., & Sale, D. G. (1993). Gender differences in strength and muscle fiber characteristics. *European Journal of Applied Physiology and Occupational Physiology*, *66*, 254–262.

Mitchell, E. A., Martin, N. R. W., Bailey, S. J., & Ferguson, R. A. (2018a). Critical power is positively related to skeletal muscle capillarity and type I muscle fibers in endurance-trained individuals. *Journal of Applied Physiology*, *125*, 737–745.

Mitchell, R. A., Schaeffer, M. R., Ramsook, A. H., Wilkie, S. S., & Guenette, J. A. (2018b). Sex differences in respiratory muscle activation patterns during high-intensity exercise in healthy humans. *Respiratory Physiology & Neurobiology*, *247*, 57–60.

Molenaar, J. P., McNeil, C. J., Bredius, M. S., & Gandevia, S. C. (2013). Effects of aging and sex on voluntary activation and peak relaxation rate of human elbow flexors studied with motor cortical stimulation. *Age (Dordrecht, Netherlands)*, *35*, 1327–1337.

Molgat-Seon, Y., Dominelli, P. B., Ramsook, A. H., Schaeffer, M. R., Sereacki, S. M., Foster, G. E., … Sheel, A. W. (2018a). The effects of age and sex on mechanical ventilatory constraint and dyspnea during exercise in healthy humans. *Journal of Applied Physiology*, *124*, 1092–1106.

Molgat-Seon, Y., Peters, C. M., & Sheel, A. W. (2018b). Sex-differences in the human respiratory system and their impact on resting pulmonary function and the integrative response to exercise. *Current Opinion in Physiology*, *6*, 21–27.

Monod, H., & Scherrer, J. (1965). The work capacity of a synergic muscular group. *Ergonomics*, *8*, 329–338.

Olesen, J., Kiilerich, K., & Pilegaard, H. (2010). PGC-1α-mediated adaptations in skeletal muscle. *Pflügers Archiv - European Journal of Physiology*, *460*, 153–162.

Olfert, I. M., Balouch, J., Kleinsasser, A., Knapp, A., Wagner, H., Wagner, P. D., & Hopkins, S. R. (2004). Does gender affect human pulmonary gas exchange during exercise? *The Journal of Physiology*, *557*, 529–541.

Oosthuyse, T., & Bosch, A. N. (2010). The effect of the menstrual cycle on exercise metabolism. *Sports Medicine (Aukland, N.Z.)*, *40*, 207–227.

Parker, B. A., Smithmyer, S. L., Pelberg, J. A., Mishkin, A. D., Herr, M. D., & Proctor, D. N. (2007). Sex differences in leg vasodilation during graded knee extensor exercise in young adults. *Journal of Applied Physiology*, *103*, 1583–1591.

Paul, S. M., & Purdy, R. H. (1992). Neuroactive steroids. *FASEB Journal*, *6*, 2311–2322.

Pereira, H. M., Schlinder-DeLap, B., Keenan, K. G., Negro, F., Farina, D., Hyngstrom, A. S., … Hunter, S. K. (2019). Oscillations in neural drive and age-related reductions in force steadiness with a cognitive challenge. *Journal of Applied Physiology*, *126*, 1056–1065.

Poole, D. C., Burnley, M., Vanhatalo, A., Rossiter, H. B., & Jones, A. M. (2016). Critical power: an important fatigue threshold in exercise physiology. *Medicine and Science in Sports and Exercise*, *48*, 2320–2334.

Poole, D. C., Ward, S. A., Gardner, G. W., & Whipp, B. J. (1988). Metabolic and respiratory profile of the upper limit for prolonged exercise in man. *Ergonomics*, *31*, 1265–1279.

Powers, S. K., & Jackson, M. J. (2008). Exercise-induced oxidative stress: cellular mechanisms and impact on muscle force production. *Physiological Reviews*, *88*, 1243–1276.

Rivero, J. L. L., Talmadge, R. J., & Edgerton, V. R. (1998). Fibre size and metabolic properties of myosin heavy chain-based fibre types in rat skeletal muscle. *Journal of Muscle Research and Cell Motility*, *19*, 733–742.

Roepstorff, C., Thiele, M., Hillig, T., Pilegaard, H., Richter, E. A., Wojtaszewski, J. F. P., & Kiens, B. (2006). Higher skeletal muscle α_2AMPK activation and lower energy charge and fat oxidation in men than in women during submaximal exercise. *The Journal of Physiology*, *574*, 125–138.

Romer, L. M., & Polkey, M. I. (2008). Exercise-induced respiratory muscle fatigue: Implications for performance. *Journal of Applied Physiology*, *104*, 879–888.

Russ, D. W., & Kent-Braun, J. A. (2003). Sex differences in human skeletal muscle fatigue are eliminated under ischemic conditions. *Journal of Applied Physiology*, *94*, 2414–2422.

Russ, D. W., Lanza, I. R., Rothman, D., & Kent-Braun, J. A. (2005). Sex differences in glycolysis during brief, intense isometric contractions. *Muscle & Nerve*, *32*, 647–655.

Scalzo, R. L., Peltonen, G. L., Binns, S. E., Shankaran, M., Giordano, G. R., Hartley, D. A., … Miller, B. F. (2014). Greater muscle protein synthesis and mitochondrial biogenesis in males compared with females during sprint interval training. *FASEB Journal*, *28*, 2705–2714.

Schaeffer, M. R., Mendonca, C. T., Levangie, M. C., Andersen, R. E., Taivassalo, T., & Jensen, D. (2014). Physiological mechanisms of sex differences in exertional dyspnoea: role of neural respiratory motor drive. *Experimental Physiology*, *99*, 427–441.

Schäfer, L. U., Hayes, M., & Dekerle, J. (2019). The magnitude of neuromuscular fatigue is not intensity dependent when cycling above critical power but relates to aerobic and anaerobic capacities. *Experimental Physiology*, *104*, 209–219.

Schaumberg, M. A., Jenkins, D. G., Janse De Jonge, X. A. K., Emmerton, L. M., & Skinner, T. L. (2017). Oral contraceptive use dampens physiological adaptations to sprint interval training. *Medicine and Science in Sports and Exercise*, *49*, 717–727.

Schiaffino, S., & Reggiani, C. (2011). Fiber types in mammalian skeletal muscles. *Physiological Reviews*, *91*, 1447–1531.

Schmitz, B., Niehues, H., Thorwesten, L., Klose, A., Krüger, M., & Brand, S. M. (2020). Sex differences in high-intensity interval training—are HIIT protocols interchangeable between females and males? *Frontiers in Physiology*, *11*, 38.

Schoene, R. B., Robertson, H. T., & Pierson, D. J. (1981). Respiratory drives and exercise in menstrual cycles of athletic and nonathletic women. *Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology*, *50*, 1300–1305.

Schwartz, J., Katz, S. A., Fegley, R. W., & Tockman, M. S. (1988). Sex and race differences in the development of lung function. *American Review of Respiratory Disease*, *138*, 1415–1421.

Senefeld, J., Pereira, H. M., Elliott, N., Yoon, T., & Hunter, S. K. (2018). Sex differences in mechanisms of recovery after isometric and dynamic fatiguing tasks. *Medicine and Science in Sports and Exercise*, *50*, 1070–1083.

Sheel, A. W., Boushel, R., & Dempsey, J. A. (2018). Competition for blood flow distribution between respiratory and locomotor muscles: Implications for muscle fatigue. *Journal of Applied Physiology*, *125*, 820–831.

Sheel, A. W., Derchak, P. A., Morgan, B. J., Pegelow, D. F., Jacques, A. J., & Dempsey, J. A. (2001). Fatiguing inspiratory muscle work causes reflex reduction in resting leg blood flow in humans. *The Journal of Physiology*, *537*, 277–289.

Sheel, A. W., Richards, J. C., Foster, G. E., & Guenette, J. A. (2004). Sex differences in respiratory exercise physiology. *Sports Medicine (Aukland, N.Z.)*, *34*, 567–579.

Sidhu, S. K., Cresswell, A. G., & Carroll, T. J. (2013). Corticospinal responses to sustained locomotor exercises: moving beyond single-joint studies of central fatigue. *Sports Medicine (Auckland, N.Z.)*, *43*, 437–449.

Sidhu, S. K., Weavil, J. C., Mangum, T. S., Jessop, J. E., Richardson, R. S., Morgan, D. E., & Amann, M. (2017). Group III/IV locomotor muscle afferents alter motor cortical and corticospinal excitability and promote central fatigue during cycling exercise. *Clinical Neurophysiology*, *128*, 44–55.

Sidhu, S. K., Weavil, J. C., Thurston, T. S., Rosenberger, D., Jessop, J. E., Wang, E., … Amann, M. (2018). Fatigue-related group III/IV muscle afferent feedback facilitates intracortical inhibition during locomotor exercise. *The Journal of Physiology*, *596*, 4789–4801.

Simoneau, J. A., & Bouchard, C. (1989). Human variation in skeletal muscle fiber-type proportion and enzyme activities. *American Journal of Physiology-Endocrinology and Metabolism*, *257*, E567–E572.

Sims, S. T., & Heather, A. K. (2018). Myths and Methodologies: Reducing scientific design ambiguity in studies comparing sexes and/or menstrual cycle phases. *Experimental Physiology*, *103*, 1309–1317.

Smith, J. R., Alexander, A. M., Hammer, S. M., Didier, K. D., Kurti, S. P., Broxterman, R. M., … Harms, C. A. (2017). Cardiovascular consequences of the inspiratory muscle metaboreflex: Effects of age and sex. *American Journal of Physiology-Heart and Cirulatory Physiology*, *312*, H1013–H1020.

Smith, J. R., Broxterman, R. M., Hammer, S. M., Alexander, A. M., Didier, K. D., Kurti, S. P., … Harms, C. A. (2016). Sex differences in the

cardiovascular consequences of the inspiratory muscle metaboreflex. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *311*, R574–R581.

Stachenfeld, N. S. (2008). Sex hormone effects on body fluid regulation. *Exercise and Sport Sciences Reviews*, *36*, 152–159.

Staron, R. S., Hagerman, F. C., Hikida, R. S., Murray, T. F., Hostler, D. P., Crill, M. T., … Toma, K. (2000). Fiber type composition of the vastus lateralis muscle of young men and women. *Journal of Histochemistry and Cytochemistry*, *48*, 623–629.

Tarnopolsky, M. A. (2008). Sex differences in exercise metabolism and the role of 17-beta estradiol. *Medicine and Science in Sports and Exercise*, *40*, 648–654.

Temesi, J., Arnal, P. J., Rupp, T., F??asson, L., Cartier, R., Gergel??, L., … Millet, G. Y. (2015). Are females more resistant to extreme neuromuscular fatigue? *Medicine and Science in Sports and Exercise*, *47*, 1372–1382.

Thomas, K., Elmeua, M., Howatson, G., & Goodall, S. (2016). Intensity-dependent contribution of neuromuscular fatigue after constant-load cycling. *Medicine and Science in Sports and Exercise*, *48*, 1751–1760.

Thomas, K., Goodall, S., & Howatson, G. (2018). Performance fatigability is not regulated to a peripheral critical threshold. *Exercise and Sport Sciences Reviews*, *46*, 240–246.

Thomas, K., Goodall, S., Stone, M., Howatson, G., Gibson, A. S. C., & Ansley, L. (2014). Central and peripheral fatigue in male cyclists after 4-, 20-, and 40-km time trials. *Medicine and Science in Sports and Exercise*, *47*, 537–546.

Tilt, E. J. (1875). The relations of women to obstetric practice. *British Medical Journal*, *1*, 73.

Torres-Tamayo, N., García-Martínez, D., Lois Zlolniski, S., Torres-Sánchez, I., García-Río, F., & Bastir, M. (2018). 3D analysis of sexual dimorphism in size, shape and breathing kinematics of human lungs. *Journal of Anatomy*, *232*, 227–237.

Van Der Vaart, H., Murgatroyd, S. R., Rossiter, H. B., Chen, C., Casaburi, R., & Porszasz, J. (2014). Selecting constant work rates for endurance testing in COPD: The role of the power–duration relationship. *COPD*, *11*, 267–276.

Vanhatalo, A., Black, M. I., DiMenna, F. J., Blackwell, J. R., Schmidt, J. F., Thompson, C., … Jones, A. M. (2016). The mechanistic bases of the power–time relationship: Muscle metabolic responses and relationships to muscle fibre type. *The Journal of Physiology*, *594*, 4407–4423.

Vanhatalo, A., Fulford, J., Dimenna, F. J., & Jones, A. M. (2010). Influence of hyperoxia on muscle metabolic responses and the power–duration relationship during severe-intensity exercise in humans: A ^{31}P magnetic resonance spectroscopy study. *Experimental Physiology*, *95*, 528–540.

Vogiatzis, I., Nanas, S., & Roussos, C. (2002). Interval training as an alternative modality to continuous exercise in patients with COPD. *European Respiratory Journal*, *20*, 12–19.

Vogiatzis, I., Terzis, G., Nanas, S., Stratakos, G., Simoes, D. C. M., Georgiadou, O., … Roussos, C. (2005). Skeletal muscle adaptations to interval training in patients with advanced COPD. *Chest*, *128*, 3838–3845.

Wagner, P. D. (1988). An integrated view of the determinants of maximum oxygen uptake. *Advances in Experimental Medicine and Biology*, *227*, 245–256.

Wagner, P. D. (1996). Determinants of maximal oxygen transport and utilization. *Annual Review of Physiology*, *58*, 21–50.

Weavil, J. C., & Amann, M. (2018). Corticospinal excitability during fatiguing whole body exercise. *Progress in Brain Research*, *240*, 219–246.

Weavil, J. C., Sidhu, S. K., Mangum, T. S., Richardson, R. S., & Amann, M. (2016). Fatigue diminishes motoneuronal excitability during cycling exercise. *Journal of Neurophysiology*, *116*, 1743–1751.

Welch, J. F., Archiza, B., Guenette, J. A., West, C. R., & Sheel, A. W. (2018). Sex differences in diaphragmatic fatigue: The cardiovascular response to inspiratory resistance. *The Journal of Physiology*, *596*, 4017–4032.

Welle, S., Tawil, R., & Thornton, C. A. (2008). Sex-related differences in gene expression in human skeletal muscle. *PLoS One*, *3*, e1385.

Westerblad, H., Bruton, J. D., & Katz, A. (2010). Skeletal muscle: Energy metabolism, fiber types, fatigue and adaptability. *Experimental Cell Research*, *316*, 3093–3099.

Woods, J. J., Furbush, F., & Bigland-Ritchie, B. (1987). Evidence for a fatigue-induced reflex inhibition of motoneuron firing rates. *Journal of Neurophysiology*, *58*, 125–137.

AUTHOR BIOGRAPHY

Paul Ansdell is a Lecturer in Exercise Physiology in the Faculty of Health and Life Sciences at Northumbria University. His PhD focused on the sex difference in fatigability of locomotor muscles, and he investigated this topic using an integrated physiological approach. His research interests include sex differences in the integration of physiological systems in acute and chronic exercise, with a view to optimizing the prescription of exercise in health and disease.

How to cite this article: Ansdell P, Thomas K, Hicks KM, Hunter SK, Howatson G, Goodall S. Physiological sex differences affect the integrative response to exercise: Acute and chronic implications. *Experimental Physiology*. 2020; 1–15. https://doi.org/10.1113/EP088548